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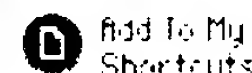
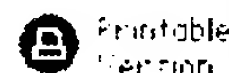
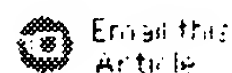
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Novel Therapeutic Agents for Systemic Lupus Erythematosus

from [Current Opinion in Rheumatology](#)

Biological Therapies

Blockade of Costimulatory Molecules (CTLA4Ig)

Upon interaction with antigen, antigen-presenting cells (APCs) express specific surface molecules, including B7. The interaction of B7 on APCs and CD28 on T cells provides an important second signal for T cell activation. **CTLA4 is expressed on activated T cells and binds B7 with higher affinity than CD28. Therefore, a fusion protein encoded by fusion of CTLA4 to an immunoglobulin cy1 chain (CTLA4-Ig) binds B7, blocks B7/CD28 interaction, and inhibits T-cell activation (Fig. 1). CTLA4-Ig blocks autoantibody production and retards autoimmune nephritis in a mouse model of lupus.**^[28] In one study, treatment of murine lupus with a combination of CTLA4-Ig and cyclophosphamide was more effective than either agent alone in blocking autoantibody production, reducing renal disease, and prolonging survival of mice with advanced nephritis.^[29] Safety data in human patients is available from two phase I studies of rheumatoid arthritis and psoriasis in which the drug was well tolerated.^[30] Furthermore, CTLA4-Ig did not increase opportunistic infection risk or affect circulating lymphocyte counts.^[31]

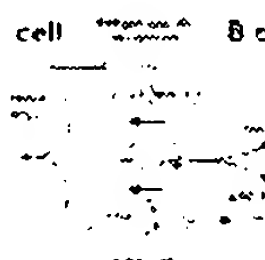


Figure 1. (click image to zoom) B and T cell costimulation

Demonstrates costimulatory molecules important for B and T cell activation. Upon interaction with antigen, antigen presenting cells (APCs), such as B cells and macrophages are stimulated to express specific surface molecules not present on resting APCs. Among these, the B7 molecules (B7-1 and B7-2) play an important role in the generation of T cell activation. The interaction of B7 on APCs and CD28 on T cells provides an important second signal for T cell activation-the first being interaction of antigen with the T cell receptor complex. While B7 is expressed on activated APCs, a molecule designated as CD40 ligand (CD40L) is expressed on activated but not resting helper T cells. CD40L binds to a complementary molecule designated as CD40 on B cells and is responsible for the production of antibodies (including autoantibodies).

Blockade of Costimulatory Molecules (Anti-CD40 Ligand)

While B7 is expressed on activated APCs, a molecule designated as CD40 ligand (CD40L) is expressed on activated but not resting helper T cells. CD40L binds to a complementary molecule designated as CD40 on B cells and is responsible for antibody production. CD40L is expressed in a higher percentage of T cells and for longer periods of time in patients with lupus compared with controls.^[32] Preliminary studies in animal models of SLE demonstrated that selective blockade of the CD40L/CD40 interaction early in life inhibits autoantibody production, reduces nephritis, and improves survival.^[33] CD40 blockade in older mice with established nephritis has also been shown to attenuate proteinuria, prolong survival, and improve renal histology.^[34] A phase I trial demonstrated that anti-CD40L mAb (IDEC-131; IDEC Pharmaceuticals, San Diego, CA) is safe and well tolerated in patients with lupus.^[35] However, a phase II study of IDEC-131 did not demonstrate clinical benefit (J. Davis, personal communication), and a study with a different monoclonal antibody to CD40L was halted because of a high incidence of thromboembolic events in treated primates.^[36] This finding could be unique to this particular agent^[37] because IDEC-131 did not show an increased risk of thrombosis in other studies.^[38] Further studies may be warranted.

Combination therapies against costimulatory pathways have been examined. In one study, CTLA-4Ig, anti-CD40L monoclonal antibody, or the combination were given to NZB/W mice for 2 weeks early in life.^[33] Survival 10 months later was 0% in the CTLA-4Ig group, 18% in the anti-CD40L group, and 70% in the combination group. This suggests that short treatment courses with combination therapy might result in a durable clinical response, a finding confirmed in a more recent study.^[39]

Anti-C5b Monoclonal Antibody

Complement plays an important role in amplifying the immune complex-based inflammatory reaction that damages the kidney in SLE nephritis. Administered to NZB/W mice, monoclonal antibody to C5 blocks the late membrane attack complex of complement (C5b-9), delays the onset of proteinuria, improves renal histology, and prolongs survival.^[40] In phase I trials in SLE and rheumatoid arthritis, a chimeric monoclonal antibody to C5 was shown to be safe and well tolerated in doses up to 8 mg/kg.^[41] Clinical trials in lupus nephritis patients are in progress.

Anti-CD20 Monoclonal Antibody (Rituximab)

CD20, a B-cell specific surface molecule, plays an important role in B-cell activation, proliferation, and differentiation. Rituximab, a chimeric mouse/human monoclonal antibody specific for the B-cell surface molecule CD20, is used in lymphoma to deplete B cells. In an ongoing phase I/II trial, rituximab has been well tolerated and has significantly depleted B-lymphocytes in 12 patients with SLE.^[42] B cell depletion correlated with improvements in rash, arthritis, fatigue, and patient genotype (F γ RIII).^[42]

Anti-Cytokine Therapy (Anti-BLyS)

The B lymphocyte stimulator (BLyS), also known as BAFF, THANK, TALL-1, and zTNF4, is a member of the TNF superfamily with profound effects on B cell immunity.^[43] BLyS stimulates lymphocyte proliferation and differentiation and increases immunoglobulin production, presumably by binding to three receptors termed TACI, BMCA, and BAFF-R.^[43] A role of BLyS in SLE has been suggested by both animal and human studies.^[44-48] Treatment of SLE mouse models with TACI-Ig fusion protein ameliorates progression of disease and improves survival.^[46] A fully human anti-human BLyS monoclonal antibody that neutralizes BLyS protein activity has been developed^[49] and is currently being tested in a phase I trial in SLE patients.

Anti-Cytokine Therapy (Anti-IL10):

Interleukin-10 (IL-10) levels are increased in patients with active SLE and correlate

with disease activity.^[50,51] In a murine SLE model, continuous administration of IL-10 accelerated onset of renal disease and treatment with an anti-IL-10 mAb delayed disease onset.^[52] A murine IgG1 anti-IL-10 mAb was given for 21 days at a dose of 20 mg/d to 6 SLE patients with active, steroid-dependent disease in an open label pilot study.^[53*] Cutaneous lesions, joint symptoms, and SLEDAI scores improved and prednisone dose was decreased. Maximal benefit was evident at 2 months, with continued responses over 3-6 months.^[53*] Phase I trials are expected with a human anti-IL10 mAb.

Section 3 of 7[Previous](#)[Continued](#)

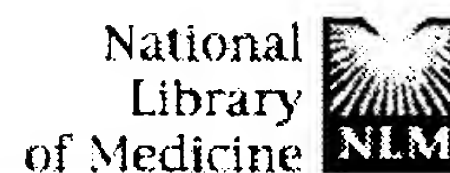
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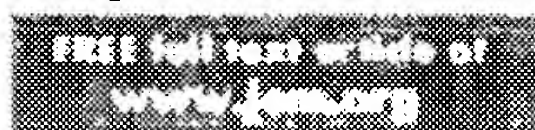


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☐ 1: J Exp Med 1998 Jul 6;188(1):199-204

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Cytotoxic T lymphocyte antigen 4 (CTLA4) blockade accelerates the acute rejection of cardiac allografts in CD28-deficient mice: CTLA4 can function independently of CD28.

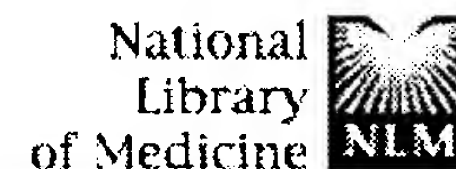
Lin H, Rathmell JC, Gray GS, Thompson CB, Leiden JM, Alegre ML

Department of Medicine, University of Chicago, Chicago, Illinois 60637, 1

Related Resources

Cytotoxic T lymphocyte antigen 4 (CTLA4) appears to negatively regulate cell activation. One mechanism by which CTLA4 might antagonize T cell function is through inhibition of CD28 signaling by competing for their shared ligands B7-1 and B7-2. In addition, CTLA4 ligation could initiate a signaling cascade that inhibits T cell activation. To address whether CTLA4 could inhibit immune responses in the absence of CD28, rejection of heart allograft was studied in CD28-deficient mice. H-2(q) hearts were transplanted into allogeneic wild-type or CD28-deficient mice (H-2(b)). Graft rejection was delayed in CD28-deficient compared with wild-type mice. Treatment of wild-type recipients with CTLA4-immunoglobulin (Ig), or with anti-B7-1 anti-B7-2 mAbs significantly prolonged allograft survival. In contrast, treatment of CD28-deficient mice with CTLA4-Ig, anti-B7-1 plus anti-B7-2 mAbs, or a blocking anti-CTLA4 mAb induced acceleration of allograft rejection. This increased rate of graft rejection was associated with more severe mononuclear cell infiltration and enhanced levels of IFN-gamma and IL-6 transcripts in donor hearts of untreated wild-type and CTLA4-Ig- or anti-CTLA4 mAb-treated CD28-deficient mice. Thus, the negative regulatory role of CTLA4 extends beyond its potential ability to prevent CD28 activation through ligand competition. Even in the absence of CD28, CTLA4 plays an inhibitory role in the regulation of allograft rejection.

PMID: 9653096 [PubMed - indexed for MEDLINE]



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☐ 1: J Immunol 1999 Oct 1;163(7):3753-7

Related Articles, L

**FREE full text article at
www.jimmunol.org****Expression of B7 molecules in recipient, not donor, mice determines the survival of cardiac allografts.**

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Mandelbrot DA, Furukawa Y, McAdam AJ, Alexander SI, Libby P, Mitchell RN, Sharpe AH.

Immunology Research Division, Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA.
dmanandelbr@bics.bwh.harvard.edu

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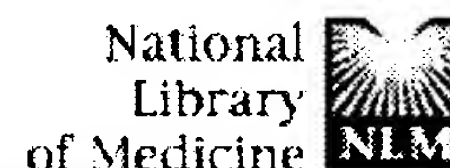
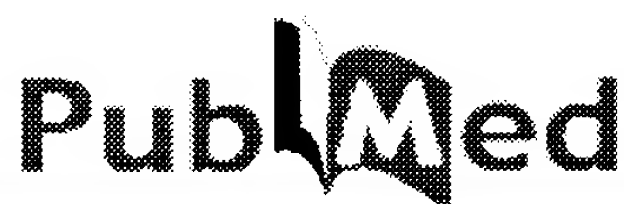
Blockade of the CD28/CTLA4/B7 costimulatory pathway using CTLA4-Ig has great therapeutic potential, and has been shown to prolong allograft survival in a variety of animal models. To gain further insight into the mechanism by which costimulatory blockade prevents allograft rejection, we studied cardiac allograft survival in the complete absence of B7 costimulation using mice lacking B7-1 and B7-2 (B7-1/B7-2^{-/-} mice). To determine the effect of B7 on donor vs recipient cells, we used B7-1/B7-2^{-/-} mice as either donors or recipients of allografts. Wild-type (WT) recipients acutely reject fully allogeneic hearts from both WT and B7-1/B7-2^{-/-} mice. In contrast, B7-1/B7-2^{-/-} recipients allow long-term survival of grafts from both WT and B7-1/B7-2^{-/-} mice, with minimal histologic evidence of either acute or chronic rejection in grafts harvested after 90 days. The B7-1/B7-2^{-/-} mice acutely reject B7-1/B7-2^{-/-} allografts if CD28 stimulation is restored by the administration of Ab to CD28 and can mount an alloresponse in mixed lymphocyte reactions. Therefore, B7-1/B7-2^{-/-} mice are capable of generating alloresponses both in vivo and in vitro. Our results demonstrate that in the alloresponse to mouse heterotopic cardiac transplantation, B7 molecules on recipient cells rather than donor cells provide the critical costimulatory signal. The indefinite survival of allografts into B7-1/B7-2^{-/-} recipients further shows that the absence of B7 costimulation alone is sufficient to prevent rejection.

PMID: 10490971 [PubMed - indexed for MEDLINE]

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1: Transplantation 1999 Feb 27;67(4):520-5

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CTLA4IgG treatment induces long-term acceptance of rat small bowel allografts.

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Tarumi K, Murakami M, Yagihashi A, Nakagawa I, Hirata K, Uede

Section of Immunopathogenesis, Institute of Immunological Science,
Hokkaido University, Sapporo, Japan.

Related Resources

BACKGROUND: CTLA4 immunoglobulin (Ig)G that binds to B7 effectively inhibits the signaling of CD28/CTLA4-B7 pathway and induces antigen specific T cell unresponsiveness in vitro and in vivo. Using CTLA4IgG, we examined induction of long-term graft survival and the mechanism of maintenance of tolerance in rat allogeneic small bowel transplantation.

METHODS: Small bowels of Brown-Norway rats (RT1n) were heterotopically transplanted into Lewis rats (RT1l). Recipients were treated with an i.p. injection of either CTLA4IgG or control IgG for 7 days.

RESULTS: Long-term survival was observed in rats treated with CTLA4IgG whereas control rats died within 16 days after transplantation. To examine whether a tolerant state was established in long-term survival rats, second transplantation was performed using small bowels of Brown-Norway rats (ACI (RT1b) rats. It was demonstrated that small bowels of Brown-Norway rats were accepted; however, those of ACI rats were rejected within 10 days. Serum concentrations of interleukin (IL)-4 were maintained at >50 microg/ml for 7 days after transplantation in rats treated with CTLA4IgG but <15 microg/ml in control rats. IL-2 concentration was reduced to half in CTLA4IgG-treated rats compared with that in control recipients. Serum IFN-gamma in CTLA4IgG-treated recipients increased after transplantation and was not distinguishable from that of control recipients during the first days after transplantation.

Conclusion: We demonstrated that CTLA4IgG treatment alone for 7 days induced a long-term donor specific tolerance in allogeneic small bowel transplantation. The induction of long-term acceptance of small bowel allografts by CTLA4IgG is not caused by simply the shift of anti-alloimmune responses from Th1 to Th2 cytokine production.

PMID: 10071020 [PubMed - indexed for MEDLINE]

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CTLA4-Ig for Autoimmune Disease

We have initiated a Phase 2 clinical trial of **CTLA4-Ig**. This study will evaluate **CTLA4-Ig** in 12 patients with refractory auto-immune thrombocytopenic purpura (ITP) in the United Kingdom. **CTLA4 Ig** is being evaluated for its ability to interrupt the body's attack on the platelets. We are currently accruing patients in this Phase 2 study which we expect to complete by year's end. ITP is an auto-immune disease in which the body makes antibodies that target a patient's own blood platelets resulting in premature platelet destruction and an impaired ability to form blood clots. The clinical consequences of ITP are largely dependent on platelet count and range from bruising, mucosal bleeding and nosebleeds to intracranial hemorrhage, which can be fatal. There are approximately 25,000 people in the United States with this condition.

CTLA4 is a T cell regulatory protein which is one of the immune system's natural "off switches". We have developed a soluble form of **CTLA4** (**CTLA-Ig**) which has immunosuppressive activity for use in organ transplantation and auto-immune diseases. **CTLA4-Ig** has the potential to inactivate only those cells that are initializing an unwanted immune response without compromising the body's ability to fight off infections. A form of **CTLA4-Ig** has been shown to be active in several clinical and non-clinical studies and was recently reported by Bristol-Myers Squibb to have activity in a Phase 2 clinical trial in 214 patients with refractory rheumatoid arthritis.







Intellectual Property

The United States Patent and Trademark Office (USPTO) has issued a Notice of Allowance on a patent application entitled "**CTLA4** -Cgamma4 Fusion Proteins". A Notice of Allowance is the final step in the patent prosecution process, which indicates that the USPTO will issue the patent. The patent, which will remain in force until 2016, covers the specific composition of the

Company's **CTLA4-Ig** product form. A **CTLA4**-Cgamma4 fusion protein is a genetically engineered form of **CTLA4** which is comprised of natural sequence **CTLA4** fused to a portion of an immunoglobulin (**Ig**) to make a soluble form of **CTLA4**. The molecule covered by the patent has additionally been engineered to eliminate those portions of the **Ig** molecule that have the potential to induce certain undesirable natural biological mechanisms, including cell lysis or cellular toxicity which may cause side effects in a patient.

Repligen and the University of Michigan (the University) previously filed a complaint against Bristol-Myers Squibb in the United States District Court for the Eastern District of Michigan seeking correction of inventorship on certain **CTLA4** related patents issued to Bristol-Myers Squibb. The suit seeks to add an inventor whose rights are assigned to the University of Michigan who was engaged in collaboration with Bristol-Myers Squibb involving, among other things, **CTLA4**. A correction of inventorship would result in the University being designated as a co-assignee on any corrected patent. Repligen is the exclusive licensee of the University of Michigan's **CTLA4** patent rights. Both Repligen and Bristol-Myers Squibb have filed motions for summary judgement. Repligen's motion requests correction of inventorship on certain Bristol-Myers Squibb patents and Bristol-Myers Squibb's motion requests dismissal of the complaint. A hearing on these motions is scheduled for the end of May during which the judge will question both parties' counsel concerning their summary motions in which each has substantiated their position for judgement based on evidence collected during the investigation of the complaint. This hearing is part of the customary legal process, following which the judge is expected to make a decision on the motions and/or on the scheduling of the trial.

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Immunomodulatory Product Candidates

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| | | Discovery | Pre-clinical | Phase I | Phase II |
| CRB-15 [®] Indications | Rheumatoid Arthritis | | | | |
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| | Psoriasis | | | | |

CARDION's Immunomodulation Program

The cornerstone of CARDION's **first platform technology "tolerance induction/immunomodulation"** is CRB-15 ("Depletin"), a **therapeutic protein targeted against the interleukin-15 receptor with potential therapeutic application in inflammatory/autoimmune disorders and transplant rejection.**

In contrast to current therapeutic efforts against inflammatory/autoimmune disorders aiming at the control of symptoms triggered by activated **immune system** cells, the application of CRB-15 has the potential to allow a more fundamental approach to disease therapy. CRB-15 targets activated **immune system** cells directly and leads to a sustained blockade of the **immune** response that triggers and perpetuates the inflammatory/autoimmune disease condition. A major CRB-15 advantage is a potential favourable safety profile. CRB-15 is likely to be highly selective in targeting the very specific subset of **immune system** cells involved in the disease. It is unlikely that CRB-15 will compromise the human body's normal capacity to fight pathogens.

CRB-15 is a fully-human fusion protein. It consists of a human IL-15 antagonist being fused to the lytic Fc-part of a human IgG1 type antibody. The antagonist module blocks further proliferation of activated **immune system** cells and preferentially drives them into programmed cell death ("apoptosis"). The Fc-part will mediate elimination of targeted cells through the innate **immune system**. This specific and efficient inhibition and elimination of activated **immune** cells will result in an improvement of the inflammatory/autoimmune disease condition for a prolonged period.

CARDION's Proprietary Stem Cell Gating Technology

Technology

General Overview

The company's **stem cell "gating technology"** is a proprietary method with the potential to reproducibly turn stem cells into pure cultures of certain fully-functioning human cells by eliminating all other cell types incl. undifferentiated proliferating cells. These populations of pure and well characterized cells can in principle be used for two different and independent applications:

- **Regenerative medicine products:** Homogeneous and pure populations of cells for transplantation are a requirement for safety and reproducible quality. In addition, uncontrolled proliferation of contaminating stem cells, with the risk of side effects or even tumor formation are reduced to a minimum if pure populations of cells obtained through gating technology are used.

- **Tool for drug screening, gene identification and target gene validation ("genomics enabler®"):** Pure populations of cells result in better readout quality (signal-to-noise ratio) in cell-based assays for use in the discovery of novel drugs as the signal-to-noise ratio improves when unwanted cells are removed.

Gating technology is a technically simple, highly-reproducible and scaleable method. In murine models, CARDION scientists have so far enabled gating technology for insulin-secreting pancreatic cells and heart muscle cells. It is reasonable to believe that gating Technology will work for other cell types and human cells as well. CARDION intends to position gating technology as one of the most important technologies for the industrialization of stem cell research.

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